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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/873,601	06/12/97	NOLAN G	A-63915/DJB/

HM12/0726
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EXAMINER	
PRASTHOFER, T	
ART UNIT	**PAPER NUMBER**
1627	28

DATE MAILED: 07/26/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File copy

Office Action Summary

Application No.	Applicant(s)	
08/873,601	NOLAN ET AL.	
Examiner	**Art Unit**	
Thomas W Prasthofer	1627	

-- Th MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

Change of Examiner

The examiner of this application has changed from T. Wessendorf to Thomas Prasthofer.

Status of the Application

Receipt is acknowledged of a request for CPA and a preliminary amendment on May 16, 2001 in paper nos. 26 and 27.

Status of the Claims

Claims 44-50 and 52-57 were pending in the present application. Claims 44-57 were cancelled and new claims 58-79 were added in Paper No. 27. Claims 58-79 are pending in the present application and are being examined on their merits.

Claims Rejections – 35 U.S.C. 101/112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 58-79 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well-established utility.

The instant specification discloses that the claimed method of screening a plurality of cells is useful "in screening methods for synthesis, identification and detection of bioactive agents which are capable of altering the phenotype of cells containing the agents (page 6, lines 10-12). The assertion in the specification cited above does not satisfy the utility requirement of 35 USC 101 and 112 (1) for the following reasons.

Applicant's claimed library method of screening a plurality of cells must satisfy 35 USC 101 and 112 (1) as defined by the statute and case law. In this regard, applicant is directed to MPEP 2107; 2107.01 and 210.02 which provide guidelines for determining the criteria for satisfying utility and enablement.

Initially it is noted that merely disclosing the ability to make a compound or compounds (e.g. a library) is in itself insufficient utility to satisfy either 35 USC 101 or 112, first paragraph as determined by the U.S. Supreme Court. . Eg. See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966). The claimed invention provides no details of how a plurality of cells are to be screened for an altered phenotype or what altered phenotypes are to be screened for. Rather, the claimed invention provides details only of the library that is contained by the cells and how that library is made.

According to the text of 35 USC sec. 101, an invention must be "useful". Our reviewing courts have applied the labels, "specific utility" (or "practical utility") to refer to this aspect of the "useful invention" requirement of sec. 101. (Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881, 883 (CCPA 1980)). In Nelson, the court characterized "specific utility" (or "practical utility") as "a shorthand way of attributing real-world value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public." (Id. at 856.) With respect to the issue of pharmaceutical utility and **vague assertions** of biological activity applicant is further directed to *In re Kirk* , 376 F.2d 936, 941, 153 USPQ 48, 52 (CCPA 1967)) and *Cross v. Iizuka* , 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985), wherein the Federal Circuit labeled applicant's assertion of "biological activity" without more specifics as a "nebulous" expression. Such statements, the court held, "convey little explicit indication regarding the utility of a compound" and do not satisfy either the utility and/or the enablement statutory requirements.

The claimed method of screening a plurality of cells does not, without further research and experimentation, provide an immediate benefit to the public for the following reasons:

The claimed method detects altered phenotypes in cells that express libraries of enzyme complexes made by joining recombinant enzymes with molecular scaffolds. The claimed method provides no screening method steps. With the exception of claims 59 and 63, all of the dependent claims limit the library contained within the cells. There are no limitations to the types of cells (other than mammalian cells in claim 63), the enzymes expressed, the "scaffolds" to be used, or the change in phenotype to be screened for. The cells can be, for example, a bacterium, a yeast cell, insect cell, plant cell, avian cell, mammalian cell, or an algae cell. Mammalian cells can be any kind of tissue culture cell or cell that is still part of a mammal, including thousands of cell tissue types from different mammals, most of which are specially adapted for particular screening methods. The enzymes can be derived from any organism and have any function. Scaffolds are nucleic acids or polypeptides of any length or sequence as long as they have binding sites for enzymes of the enzyme complex. The change in phenotype can be any change including, for example, cell death, prevention of cell death, altered ability to grow on or in a particular medium, antibiotic resistance, antibiotic sensitivity, tumorigenesis, cell proliferation, cell differentiation, cell dedifferentiation, the ability to produce a product, and change in cell morphology.

Given the breadth of the claimed invention, it is a certainty that one of ordinary skill practicing the invention could screen a plurality of cells and find one with an altered phenotype. This does not provide an immediate benefit to the public, however, because the significance of the change in phenotype as well as the cells, enzymes (and expression vectors), scaffolds, and change in phenotype are left for one practicing the invention to determine. In other words, the claimed invention does not have a specific and/or substantial utility because the utility is left for one using the claimed invention to determine.

In the absence of an asserted specific utility, the "useful" requirement may be established by reference to a well-established utility. A "well established-utility" is a "specific utility" which is well known, immediately apparent and implied by the specification based on the

disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

The claimed method of screening is not supported by a well established utility, however, because neither the specification as filed nor any art of record discloses or suggests any detected change in cell phenotype would establish that the associated enzyme complex has a well established utility.

In the present instance, applicant's asserted utility, e.g. for someone else (other than applicant) to use the presently claimed method to identify enzyme complexes for use in candidate drug screening clearly represents an invitation to experiment. *See Brenner v. Manson* cited above. The specification fails demonstrate the use of the claimed method to identify (by screening) a single enzyme complex that can be used to screen candidate drugs for a particular activity.

Accordingly, the lack of specification teaching regarding what combinations of enzyme complexes, scaffolds, cells, and phenotype changes may be used to identify enzyme complexes to be used in a drug candidate assay necessarily places undue experimentation on the public to determine the claimed invention's utility.

2. Claims 58-79 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims Rejections – 35 U.S.C. 112, first paragraph

3. Claims 58-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (Written Description).

With respect to adequate disclosure of the scope of the presently claimed generic applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* U.S. Court

of Appeals Federal Circuit (CA FC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997 No. 96-1175 regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* which provide reasonable assurance to one skilled in the art that the claimed method is enabled and that *applicant had possession of the full scope of the claimed invention*, i.e. a method of screening a plurality of cells for a change in phenotype. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Unlike *Lilly*, applicant **does not** HAVE A SINGLE EXAMPLE of a plurality of cells that has been screened for an altered phenotype and thus does not provide even a single species in support of a potentially broad generic of different and nonexemplified cells, enzymes, scaffolds, and altered phenotypes, which generics are much broader than the *Lilly* generic invention.

Like *Lilly*, applicant asserts that there is a means of obtaining these cells, enzymes, scaffolds, and altered phenotypes; however, this is not relevant to the disclosure requirement in which the applicant must demonstrate possession of the claimed scope at the time of filing.

4. Claims 58-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (New Matter).

A. New claim 58 recites a method of screening a plurality of cells in which step (a) is "producing a plurality of cells comprising a library of nucleic acids encoding a library of exogenous scaffolds;" and step (b) is "introducing into said plurality of cells a library of nucleic acids each encoding at least a first enzyme and a second enzyme." In this claim it appears that step (a) must be performed before and independently of step (b). The original claims and specification do not appear to support this requirement and instead indicate that scaffold sequences are fused with other sequences, indicating that they are introduced into the cell along with enzyme encoding sequences. Applicant can overcome this rejection by pointing out where

support for the requirement of performing method step (a) before and independently of method step (b) can be found in the application as originally filed.

B. New claim 58 is written does not recite the screening for bioactive agents but only screening for a change in cell phenotype. The original claims and specification do not appear to support this omission. Applicant can overcome this rejection by pointing out where support for omitting bioactive agents can be found in the application as originally filed.

C. New claim 73 recites "a method according to claim 58 further comprises isolating said scaffold from said cell exhibiting an altered phenotype." The original claims and specification do not appear to support this limitation. Applicant can overcome this rejection by pointing out where support for this limitation can be found in the application as originally filed.

D. New claim 74 recites "a method according to claim 58 further comprises isolating said nucleic acid encoding said scaffold from said cell exhibiting an altered phenotype." The original claims and specification do not appear to support this limitation. Applicant can overcome this rejection by pointing out where support for this limitation can be found in the application as originally filed.

Claims Rejections – 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 58-79 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: definite method steps required for screening cells such as detecting a change in phenotype, placing cells in an environment and/or contacting the cells with reagents required for the screening steps.

6. Claims 58-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 58 recites the term "exogenous scaffolds." It is not clear what the metes and bounds of the claimed invention are with respect to structures of nucleic acids and peptides (or proteins) that are "exogenous scaffolds." There are no limitations with respect to nucleic acid or amino acid sequences, the lengths of the scaffolds or how one is to determine whether or not the scaffolds possess binding sites specific for the enzymes in the claim.

B. Claim 59 recites the term "exogenous bioactive agent precursor." It is not clear what molecules are encompassed by the term so it is not possible to determine the metes and bounds of the claimed invention. For example, all cell cultures include growth media that comprise nutrients such as amino acids, carbohydrates, peptides, and vitamins, hormones, and serum, for example. One of ordinary skill in the art would not know how to differentiate between exogenous bioactive agent precursors and components of the growth media.

C. It is not clear what structures the term "targeting sequence" in claim 65 is intended to include and/or exclude. From the description of the term in the specification (page 17, lines 12-20), it appears that any nucleic acid that encodes a binding site on a scaffold that binds to an enzyme can be a targeting sequence. Since the function of the scaffold is to bind to enzymes, it appears that all nucleic acids encoding scaffolds automatically include targeting sequences. The description of targeting sequences gives non-limiting examples of what sequences are targeting sequences but does not provide one of ordinary skill in the art the information required to determine the metes and bounds of the claimed invention.

D. It is not clear what the metes and bounds of the term "rescue sequence" are in claim 66. Any epitope on a protein or any sequence in a nucleic acid can be used to isolate or purify the protein or nucleic acid. It is not clear, for example, if known epitopes that known antibodies bind to are "rescue sequences" or if any known nucleic acid sequence is to be included because knowing the sequence automatically allows for isolation using complementary RNA or DNA.

E. It is not clear what the metes and bounds of the term "stability sequence" are in claim 67. For example, it is not clear if poly A tails, G caps, 5' and 3' non-translated sequences and

glycosylation sites are to be included. One of ordinary skill in the art would not be able to determine the metes and bounds of the claimed invention.

F. Is not clear what the differences are between a "localization signal" and a "targeting sequence.

Claims Rejections – 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. Claims 58, 59-62, 64-66, 68, 69, 72, 77, and 78 are rejected under 35 U.S.C. 102(e) as being anticipated by Khosla et al. U.S. Patent No. 5,672,491, September, 1997 (filed May 6, 1994).

The Khosla et al. reference discloses methods for producing novel polyketides using recombinant DNA techniques (abstract). Polyketide synthases (PKSs) are multifunctional enzyme complexes composed of multiple polypeptide chains (column 1, lines 41-64). With regard to the presently claimed invention, one of the polypeptides in the multi-enzyme complex is considered to be a "scaffold" and has binding sites for at least two other polypeptides in the enzyme complex. Cells are produced which comprise libraries of recombinant (exogenous) PKS gene clusters that encode a plurality PKS polypeptides (column 3, line 37-column 4, line 13). Reference method steps (a) and (b) involve a donor plasmid and a recipient plasmid. The donor plasmid, for example can contain genes that encode enzyme components of a PKS complex that are considered to be "exogenous scaffolds" while the recipient plasmid contains nucleic acids that encode other enzymes of the PKS synthase. Cells are screened for the altered phenotypes of resistance to antibiotics or production of polyketides (column 10, lines 18-32, column 12, lines 51-57, and example 5). Accordingly, the Khosla et al. reference anticipates present claim 58.

The growth media used for the propagation of cells includes nutrients required for growth and starting materials for the synthesis of polyketides, anticipating present claim 59 (contacting cells with exogenous bioactive precursors). The polypeptides of the PKS enzyme complex (including the scaffold) are linear polymers of amino acids, anticipating present claim 64.

The present specification described "target sequences" as "binding sequences capable of causing binding of the expression product to a predetermined molecule." Since all of the recombinant enzymes in the enzyme complex bind to other enzymes of the enzyme complex, each nucleic acid encoding an enzyme of the complex includes a target sequence, anticipating present claims 65 and 68.

Page 22 of the present specification describes a "rescue sequence" as "a sequence which may be used to purify or isolate either the scaffolds, enzymes, or enzyme complex, or the nucleic acids encoding them." Column 19, lines 28-36 of the reference disclose that PCR was used to amplify (isolate) PKS genes. The binding sites for PCR primers are encompassed by the description of "rescue sequence" in the specification, anticipating present claim 66 and 69.

Column 28, lines 20-31 disclose that colonies of cells that had become resistant to carbenicillin and chloramphenicol and produced polyketides were restreaked, anticipating present claim 72. The altered phenotype of resistance to antibiotics requires precursor molecules (bioactive agent precursors) in the growth medium (e.g. propionate, column 28, line 45), anticipating present claim 77. Column 28, lines 43-60 disclose the identification of a polyketide produced by a cell, anticipating present claim 78. Column 8, lines 46-52 of the Khosla et al. reference discloses more than eight different kinds of enzymes that can comprise a PKS enzyme complex. One of ordinary skill in the art would immediately envisage multiple binding sites on one or more of the enzymes in the complex for one or more other enzymes in the complex so that two, three, four, or five binding sites would be envisaged on one enzyme. This reads on up to five binding sites on a scaffold, anticipating present claims 60-62.

8. Claims 58, 59, 63-70, and 74-79 are rejected under 35 U.S.C. 102(e) as being anticipated by Minshull et al. U.S. Patent No. 5,837,458 November 1998(filed May, 1996) with Srere

(1987) Annual Review of Biochemistry 56:89-91 cited in support of the inherency of "scaffolds."

The Minshull et al. reference discloses a method of genetic molecular evolution Abstract). Column 2, lines 38-62 disclose the production and screening of recombinant libraries that confer the ability to catalyze a reaction of interest (i.e. libraries that encode enzymes and screening for cells that have the altered phenotype of catalyzing a reaction.) At least a first and second DNA from at least one gene are recombined, indicating that two or more genes encoding at least a first enzyme and a second enzyme are introduced into cells. The Minshull et al. reference also discloses that the method can be used for the evolution of entire pathways including polyketide synthesis pathways (column 6, line 49-column 7, line 43 and column 29). Other pathways that produce antibiotics and amino acids are also taught as being "evolved" by the method of Minshull et al. (columns 25 and 33). With respect to present claim 58, the Minshull et al. reference explicitly discloses all of the claimed invention except for the presence of an exogenous scaffold.

The presence of an "exogenous scaffold" is inherent in several embodiments of Minshull et al. Polyketides are known to by synthesized by polyketide synthase enzyme complexes that are made of multiple polypeptide enzymes joined together through noncovalent interactions (column 6, line 49-column 7, line 43 and column 29). Any one of the recombinant enzymes in the enzyme complex can be an "exogenous scaffold," as defined in the present specification.

The Srere reference discloses that the synthesis of antibiotics and the synthesis of amino acids are both performed by enzyme complexes. Other well-known pathways are also disclosed by Srere as being catalyzed by large enzyme complexes as well.

Since Minshull et al. discloses a method for the simultaneous evolution of entire pathways (i.e. all of the enzymes involved in a pathway) and at least three of the disclosed pathways inherently include enzymes that meet the definition of "exogenous scaffold," Minshull anticipates present claim 58. Although Minshull et al. do not specifically disclose the isolation and identification of a polyketide, one of ordinary skill in the art would immediately have envisaged doing so because polyketide antibiotics are useful drugs that are administered after isolation and purification. Accordingly, the reference anticipates present claim 78.

Column 13, lines 31-46 of the Minshull et al. reference discloses the use of mammalian cells, anticipating present claim 63. The polypeptides comprising enzymes within enzyme complexes (including the scaffold) are linear and include binding sites for other enzymes of the complex (targeting sequences), anticipating present claims 64, 65, and 68. PCR amplification of DNA fragments to introduce homology sequences into gene clusters is disclosed in column 6, lines 49-66, anticipating present claims 66 and 69 because the primer sequences can be used to recover the DNA that encodes a scaffold. Mammalian cells must be grown in media that includes nutrients and serum, for example that are used as precursors of bioactive agents such as antibiotics or amino acids, anticipating present claims 59 and 77. Expression of genes that encode enzymes inherently includes polyadenylation signals, anticipating present claims 67 and 70. Proteins expressed in mammalian cells are normally localized to one compartment (i.e. cytosol, mitochondrial matrix, golgi lumen or membrane etc.) so all nucleic acids that encode recombinant enzymes have some kind of localization signal, anticipating present claim 79. Example 1, column 36 discloses the isolation of plasmid DNA from individual colonies (i.e. DNA encoding scaffold and enzymes), anticipating present claims 74 and 76. The generation of enzymes (as opposed to cells containing enzymes) that catalyze reactions of interest is disclosed in column 13, lines 9-16, anticipating present claim 75.

Claims Rejections – 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 71 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Minshull et al. U.S. Patent No. 5,837,458.

The Minshull et al. reference discloses a method of genetic molecular evolution Abstract). Column 2, lines 38-62 disclose the production and screening of recombinant libraries

that confer the ability to catalyze a reaction of interest (i.e. libraries that encode enzymes and screening for cells that have the altered phenotype of catalyzing a reaction.) At least a first and second DNA from at least one gene are recombined, indicating that two or more genes encoding at least a first enzyme and a second enzyme are introduced into cells. The Minshull et al. reference also discloses that the method can be used for the evolution of entire pathways including polyketide synthesis pathways (column 6, line 49-column 7, line 43 and column 29). Other pathways that produce antibiotics and amino acids are also taught as being "evolved" by the method of Minshull et al. (columns 25 and 33). With respect to present claim 58, the Minshull et al. reference explicitly teaches all of the claimed invention except for the presence of an "exogenous scaffold."

The presence of an "exogenous scaffold" is inherent in several embodiments of Minshull et al. Polyketides are known to by synthesized by polyketide synthase enzyme complexes that are made of multiple polypeptide enzymes joined together through noncovalent interactions (column 6, line 49-column 7, line 43 and column 29). Any one of the recombinant enzymes in the enzyme complex can be an exogenous scaffold, as defined in the present specification.

Minshull et al. teaches that virus-virus recombination involving viruses that are not lethal to the host cell and virus-chromosome recombination can be used in their method (column 10 lines 55-65 and column 12, lines1-22). Minshull et al. do not explicitly teach the use of retroviral infection.

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use a retroviral vector in the method of Minshull et al. One would have been motivated to do so because retroviral vectors are commonly used to transform cells, are usually not lethal when they are used to introduce recombinant DNA into chromosomes. One would have had a reasonable expectation of success because the use of retroviral vectors was routine in the art at the time that the invention was made.

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to isolate individual enzymes of the enzyme complex (including the scaffold) either directly or indirectly by isolating the nucleic acid encoding the enzyme. One would have been motivated to do so, for example, in order to fully characterize the enzyme (scaffold) by SDS-PAGE, to raise antibodies, to crystallize the enzyme, and/or conduct enzyme kinetics. One

would have had a reasonable expectation for success because enzyme purification and analysis were routine in the art and other PKS enzymes had already been purified and studied.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas Prasthofer** at telephone number **(703) 308-4548**. The examiner can normally be reached on Monday, Tuesday, Friday, and Saturday 8:00-6:30.

10. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

11. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.

Thomas Prasthofer, Ph.D.

July 20, 2001

BENNETT CELSA
PRIMARY EXAMINER